REMARKS

Claims 1-40 are pending in the instant application. Claims 1-9 and 22-31 have been rejected. Claims 10-21 and 32-40 have been allowed. Claims 1, 2 and 5 have been amended. Support for these amendments can be found in the specification on page 17, lines 16 and 26-28.

Rejection of Claims 1-9 and 22-31 under 35 USC §112, first paragraph

The Examiner has rejected Claims 1-9 and 22-31 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner stated that:

> The specification, while being enabling for non-heterocyclic substituted 1,2,9,9-tetrahydro-3H-fluoren-3-ene compounds, does not reasonably provide enablement for heterocyclic substituted derivatives other than pyridine, piperidine, thienyl, imidazole, pyrazole, oxazole, isoxazole, thiazole, pyrrole, morpholne, furyl, pyridazine, pyrimidine, purazinyl, benzimidazole, indole, purine and thiazole, in particular, N-heterocyclic derivatives, were prepared or obtained. The process of making the heterocyclic substituted derivatives or how the heterocyclic derivatives were obtained is not readily apparent from the specification. The specification must teach how to make the invention, In re Gardner, 166 USPQ 138 (1970). In order to practice the claimed invention, one skilled in the art would have speculate how the derivatives were obtained or prepared. There is insufficient disclosure of starting materials that would place such a diverse genus of compounds in possession of the public in the event of a patent grant. In addition, there is no reasonable assurance that such an alleged genus of compounds would possess all of the alleged properties for use. See In re Fouche 169 USPQ 429 (CCPA 1971). Therefore, the instant invention is not enabled. Claims limiting the scope of these terms should overcome this rejection.

Applicants respectfully traverse this rejection. Applicants assert that the specification does enable the claims and provides ample guidance as to how substituted heterocyclic derivatives are prepared. After reading Applicants' specification, one skilled in the art would be able to prepare the compounds of the present invention, including the heterocyclic derivatives, and would be able to obtain appropriate starting materials to make said compounds. However, to advance the prosecution of the present application, Applicants have amended the claims to replace the terms "heterocycloalkyl" and "heteroaryl" with the specific hetercycloalkyl and heteroaryl groups named in the specification.

Accordingly, Applicants respectfully request the rejection of claims 1-9 and 22-31 under 35 USC §112, first paragraph, be withdrawn.

Rejection of Claims 1-9 and 22-31 under 35 USC §103(a)

The Examiner has rejected Claims 1-9 and 22-31 under 35 USC §103(a), as being unpatentable over Cragoe Jr. *et al.*, U.S. 4,731,471 and/or Conn *et al.*, U.S. 4,704,472. Specifically, the Examiner stated that:

> Both Cragoe Jr. et al and Conn et al both teach fluorenone derivatives as claimed. Patentees differ in that all of the species encompassed by the recited claims. However, it would have been obvious to one of ordinary skill in the art to modify the teachings of the cited references to obtain other analogous compounds such as the, for example, heterocyclic substituted analogous compounds claimed.

Applicants respectfully traverse this rejection. As noted by the Examiner, the compounds of the instant invention differ from those described in Cragoe Jr. and Conn. However, the Examiner alleges that it would have been obvious to one skilled in the art to modify these teachings to obtain other analogous compounds, such as heterocyclic analogues. Applicants respectfully disagree with this conclusion because Cragoe Jr. et al. and Conn et al. teach fluorenone derivatives that are distinct from the fluorenone derivatives in the instant application in both form and function.

Applicants claim compounds that can have a heterocyclic substitution at R^3 (position 4 on the tetrahydrofluorenone ring system) and R^{10} (position 9a on

the tetrahydrofluorenone ring system). Cragoe Jr. does not teach any substitution at position 4 on the tetrahydrofluorenone ring system. At position 9a on the tetrahydrofluorenone ring system, Cragoe Jr. teaches C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} acyloxyalkyl or C_{1-6} alkoxyalkyl. Similarly, Conn teaches an unsubstituted position 4 and propyl substitution at position 9a. Thus, the compounds in the instant application differ from those of Cragoe Jr. and Conn in form.

With regard to function, Cragoe Jr. teaches that the compounds disclosed therein are useful in the treatment of brain edema. Included in the patent are references to assays that can be used to demonstrate the intrinsic activity of the compounds disclosed therein to inhibit the swelling of brain tissues (see Cragoe Jr., column 15, lines 25-37). Cragoe Jr. further teaches at column 3, lines 24-35, that:

> The compounds of this invention are of particular value since the novel functional 9a-substituent is designed to import highly desirable properties. The unique character of these substituents is intended to impart increased capability to cross the blood-brain barrier while retaining potent intrinsic anti-edemic activity. The 9a-substituents were selected for their known ability to affect lipophilicity, protein binding, etc. which are known to influence the tendency of drugs to cross the blood-brain barrier.

Essentially, Cragoe Jr. teaches how to make fluorenone derivatives with specific substitution patterns. Cragoe Jr. teaches that these derivatives are useful in the treatment of brain edema, and explains that the desired anti-edemic activity is achieved due to the *novel functional 9a-substituents* disclosed. Clearly, one skilled in the art would not look to Cragoe Jr. for instruction in modifying or making selective estrogen receptor modulators.

Similarly, Conn teaches the direct preparation of enantiomers of a substituted fluorenyloxyacetic acid. Conn discloses that the fluorenyloxyacteic acid disclosed therein are useful for the treatment of brain edema. Conn does not teach how to make the compounds of the instant invention.

Thus, one skilled in the art would not be motivated to modify Cragoe Jr. or Conn, separately or together, to synthesize the selective estrogen receptor

modulators of the present invention, including any heterocyclic derivatives. Applicants maintain that the application is in condition for allowance and passage to issue is earnestly requested.

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this response to Merck Deposit Account No. 13-2755.

Respectfully submitted,

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